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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,567	05/02/2002	Dan L. Eaton	P3230R1C47	9763

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EXAMINER

KEMMERER, ELIZABETH

ART UNIT PAPER NUMBER

1646

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/063,567

Applicant(s)

EATON ET AL

Examiner

Elizabeth C. Kemmerer, Ph.D.

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 08 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 14-16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 May 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of Application, Amendments, And/Or Claims***

Upon further consideration, and in order to make several new references of record in support of the standing utility and enablement rejections, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicant can request a refund for the associated fee or leave it as credit for future appeals. The delay and inconvenience to Applicant is regretted.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner Elizabeth C. Kemmerer.

### ***35 U.S.C. §§ 101 and 112, First Paragraph***

Claims 14-16 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to isolated polypeptides corresponding to SEQ ID NO: 60, referred to in the specification as PRO1291. The specification does not disclose any secondary or tertiary structural features of this polypeptide, nor does it assert that the polypeptide has any homology with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1291 such as subcellular location, timing of regulation during cellular differentiation, which hormones

or transcription factors regulate PRO1291, and what physiological significance PRO1291 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

The record shows that Applicant relies primarily upon the asserted utility disclosed in Example 18, namely, that the claimed polypeptides are useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of having a tumor (see, for example, p. 6 of the response received 09 August 2004; pp. 8-9 of the Appeal Brief received 08 June 2005). However, this asserted utility is not substantial for the following reasons.

In Example 18, the specification discloses that PRO1291 tested positive in a differential tissue expression analysis to detect overexpression of PRO polypeptides in cancerous tumors (pp. 140+). Quantitative PCR was used to detect differences in levels of cDNAs in cDNA libraries made from cancerous and normal tissues. Example 18 discloses that PRO1291 cDNA levels are: 1) higher in esophageal tumor as compared to normal esophagus; 2) higher in lung tumor as compared to normal lung; and 3) higher in normal skin as compared to melanoma tumor. There is no disclosure of how great a difference in cDNA levels was detected. While this disclosure may provide utility and enablement for PRO1291 DNA, it does not provide utility nor enablement for PRO1291 polypeptides or antibodies. The literature indicates that changes in mRNA levels are not predictive of changes in the encoded polypeptide levels, especially in cancerous cells. For example, Hu et al. (2003, *Journal of Proteome Research* 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference

Art Unit: 1646

in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (2003, *Nature Biotechnology* 21:976-977). Similarly, Chen et al. (2002, *Molecular and Cellular Proteomics* 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312).

The art also shows that transcript levels do not necessarily correlate with protein levels in normal tissues. See Haynes et al. (1998, *Electrophoresis* 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes,

Art Unit: 1646

equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, *Mol. Cell. Biol.* 19:1720-1730) conducted a similar study with over 150 proteins. They concluded that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (Abstract). Lian et al. (2001, *Blood* 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, *J. Biol. Chem.* 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

Thus, in the absence of information regarding whether or not PRO1291 protein levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1291 **polypeptides** as diagnostic markers and therapeutic targets are

Art Unit: 1646

simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 14-16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (571) 272-0829. The fax phone

Art Unit: 1646

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK

A handwritten signature in black ink, reading "Elizabeth C. Kemmerer". The signature is written in a cursive style with a large, stylized 'E' and 'K'.

ELIZABETH KEMMERER  
PRIMARY EXAMINER